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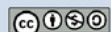
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ABSTRACT

Introduction: Pulpal inflammation can be marked by an increase in tumor necrosis factor- α (TNF- α), malondialdehyde (MDA) and calcitonin gene-related peptide (CGRP) level. Epigallocatechin-3-gallate (EGCG) demonstrates the ability to reduce cytokine expression, influence immune receptors, reduce inflammation, neutralize reactive oxygen species (ROS) and to inhibit pain conduction. The present research aimed to determine the anti-inflammatory, antioxidant and pain conduction inhibition of topical EGCG hydrogels in Lipopolysaccharide (LPS)-induced pulpal inflammation in rats. **Methods and Materials:** A total of 28 male Wistar rats were divided equally into four groups. The negative control group (N) received no treatment, while the positive control group (C) and the other two treatment groups (T1, T2) were induced with LPS for 6 h, followed by the application of topical polyethylene glycol (PEG) hydrogels for C group, 25 ppm EGCG hydrogels for T1 group and 75 ppm EGCG hydrogels for T2 group, before being filled with glass ionomer cement (GIC). After 24 h, PEG and EGCG were reapplied and refilled with GIC for 24 h. The pulp tissue samples were examined by means of immunohistochemistry (IHC) to identify TNF- α , MDA and CGRP expression. All the data obtained was analyzed with one-way analyses of variance (ANOVA) test. **Results:** The T1 and T2 groups showed a significant decrease in TNF- α and CGRP expression compared to the control group, but there was no significant decrease in MDA in either group ($P < 0.05$). **Conclusion:** Based on the results of this study, topical application of 75 ppm EGCG hydrogels to the tooth cavities with six hours of pulpal inflammation has the optimal result in reducing the expression of TNF- α and CGRP, but not of MDA.

Keywords: Calcitonin Gene-related Peptide; Epigallocatechin-3-Gallate; Malondialdehyde; Pulpal Inflammation; Tumor Necrosis Factor- α

Introduction

The most frequent case for patients to visit a dental clinic often involves pulpal inflammation with the manifestation of sharp tooth ache. The accumulation of *Escherichia coli* (*E. coli*) lipopolysaccharide (LPS) induces pulpal inflammation and an up-regulated transient receptor potential vanilloid (TRPV1) could contribute to hyperalgesia [1]. LPS can infiltrate exposed dentin to the pulpal chamber through the

fluid movement in the dentin tubules and pulpal chamber causing pathologic changes in the pulp [2]. During inflammation, the release of tumor necrosis factor- α (TNF- α) was up-regulated, producing an excessive intracellular reactive oxygen species (ROS) [3, 4]. TNF- α expressions are known to increase 6 h after LPS induction and will reach a peak 24 h later [5]. ROS can damage cellular lipids, causing poly unsaturated fatty acid (PUFA) peroxidation, which results in malondialdehyde (MDA) [6]. On the first three days, acute

pulpitis displays a broad hemorrhagic necrosis and significant accumulation of inflammatory cells, while, after 5 days, almost all of the tissue becomes necrotic [5]. TNF- α is able to activate TNF- α receptors (TNFR) located on the surface of neuron cells and stimulate substance P (SP) and calcitonin gene-related peptide (CGRP) release [7, 8]. Pulpal nerve fibers contain neuropeptide SP and CGRP, which are released an hour after injury which resulted in the conduction of pain impulses throughout the sensory neuron membrane [9-11].

The escalation of inflammation, which can lead to necrotic pulp conditions, are usually found in non-immediate treated patients with pulpal inflammation. Hence, early intervention, as vital pulp therapy (direct pulp capping, partial pulpotomy and pulpotomy), and pulp sedative, is necessary in order to prevent an increase in inflammation, more extensive pain and a worsening condition [12-15]. Generally, the most commonly used pain relief consists of eugenol (clove oil), creosote, procaine, phenol and chloroform and several corticosteroids combined with polyantibiotics. However, they are known to have a high level of toxicity, especially eugenol [15, 16].

Epigallocatechin-3-gallate (EGCG), a catechin group of polyphenolic substances which represents one of the four major green tea flavonoids, has the ability in scavenging ROS directly and indirectly reducing inflammation, stimulating the expression of antioxidant endogens and possesses antibacterial and analgesic properties [17-19]. Flavonoid, in general, was known for its antioxidant, anticarcinogenic, antimutagenic and anti-inflammatory properties [20]. EGCG has a non-polar or hydrophilic characteristic which helps to infiltrate cytoplasm and the cell nucleus by diffusing through the protein pore channel in the cell membrane and interacting with intracellular molecules [21]. Previous studies have confirmed that EGCG could block toll-like receptor 4 (TLR4), thus inhibiting TNF- α expression and free radical activities which will prevent lipid membrane oxidation, membrane damage and a decrease of prostaglandin-E2 (PG-E2) production [22, 23]. It also could reduce pain by preventing the opening of a voltage-gated sodium (Na⁺) ion channel [18]. This indicates that inflammation can be reduced after the administration of EGCG which could act as an antioxidant and analgesic.

The research conducted by Weisburg *et al.* [24] confirmed that EGCG was toxic at a concentration of 50 μ M to human gingival epithelial (S-G) cells and 150 μ M to normal human gingival 56 (GN56) fibroblasts. The absorption of drugs in liquid form was greater and more rapid, but was effective for shorter durations compared to paste, cream or gels [25]. The gel form preparation could be used as a drug delivery system due to its ability to control drug release and to protect the drug from a harsh

environment [26]. The most widely-used gel basis is Polyethylene Glycol (PEG) as it provides a controlled, continuous, stable and widespread drug release with low toxicity [27].

This research was intended to determine the anti-inflammatory, antioxidant, and pain conduction inhibition of the 25 ppm and 75 ppm topical EGCG hydrogels in *E. coli* LPS-induced pulpal inflammation in rats.

Materials and Methods

Experimental design

Ethical clearance was approved by the Health Research Ethical Clearance Commission, Faculty of Dental Medicine, Universitas Airlangga, No. 018/HRECC.FODM/ III/2018. This study was an experimental laboratory study using 28 healthy male Wistar rats (*Rattus norvegicus*) with approximately 10 weeks of age, and weighing 220-300 gr as animal subjects. The samples were equally divided into four groups ($n=7$): a negative control group (N) which received no treatment; a positive control group (C) which received cavity preparation and 6 h LPS application followed by administration of PEG hydrogel for 2 \times 24 h; and two treatment groups, which received cavity preparation and 6 h LPS application prior to being treated with 25 ppm (T1) and 75 ppm (T2) of EGCG hydrogels for 2 \times 24 h.

Cavity preparation

In group C, T1 and T2 were anesthetized by means of a 0.2 cc intra-muscular injection of a mixture of Ketalar[®] ketamine (Warner Lambert, Dublin, Ireland) and Xyla[®] xylazine base (PT Tekad Mandiri Citra, Bandung, Indonesia) with ratio 1:1.

Class I preparation was performed on the lower right first molar tooth using a high-speed drill with a 0.3 mm fissurotomy bur (SS White burs Inc., Lakewood, USA) under water cooling. The preparation was carried out to create open dentinal tubules with minimal damage to the pulp and avoid exposure of the pulp horn. To dry the cavity and confirm the absence of bleeding, which is a sign of pulp horn exposure, a fine paper point was used [1].

Induction of pulpal inflammation

Pulpal inflammation induction in groups C, T1 and T2 was performed using topical LPS (derived from *Escherichia coli*, serotype 0111: B4, Sigma Chemical Co, St. Louis, USA; product number L2630) for 6 h. Irrigation of the cavities was carried out by means of sterile saline solution prior to drying with a sterile cotton pellet. The application of 0.5 μ L LPS at a concentration of 10 μ g/ μ L, was completed, without overfilling the cavity, using a fine, flattened, 0.5 mm diameter micro-brush (Microbrush, Grafton, USA) before being allowed to dry. This wet and dry

procedure was repeated 6 times [1], before the cavity was finally covered with Glass Ionomer Cement (GIC) (Fuji 7, GC Corp, Tokyo, Japan).

Application of topical EGCG

PEG hydrogel was produced by mixing 80% PEG 400 with 20% PEG 4000 (Sigma-Aldrich, St. Louis, USA; CAS Number: 25322-68-3). EGCG hydrogel was produced by mixing EGCG (Xi'an Rongsheng Biotechnology Co., Ltd., Shaanxi, China, batch number 2013101512 RS) with 80% PEG 400 and 20% PEG 4000.

In C group, only PEG hydrogel was applied, while 25 ppm and 75 ppm of EGCG hydrogels were consecutively applied to T1 and T2 groups. After the application, the cavities were filled with GIC. After 24 h, PEG hydrogels, as well as 25 ppm and 75 ppm EGCG hydrogels were re-applied to each group before being re-covered with GIC.

Immunohistochemistry staining

The Wistar rats were sacrificed 24 h after completion of the treatment, in order to obtain analysis specimens, by surgically removing the lower right first molar tooth along with the jaw. The mandibula were decalcified with 10% ethylenediamine tetraacetic acid (EDTA) at pH 7.4, with the solution being replaced every 3 days during the 30 days of immersion at room temperature. The samples were taken from the dental pulp of the teeth. Immunohistochemistry (IHC) staining was performed by means of anti-rat TNF- α monoclonal antibodies (Santa Cruz Biotechnology Inc., Dallas, USA; catalog number: sc 52746), anti-rat MDA monoclonal antibodies (Abcam, Cambridge, USA; catalog number: ab 6463), and anti-rat CGRP monoclonal antibodies (Santa Cruz Biotechnology Inc., Dallas, USA; catalog number: sc-8857).

Each specimen was observed by two experts. Observers examined blank specimens without any grouping and interventional information data was provided. Specimens were observed by a light microscope E 100 under 400 \times magnification from five perspective points. The image was used to calculate the surface area of the cells. The presence of TNF- α , MDA macrophage cells and CGRP sensory nerve cell expressions in each group were noted. A digital camera (A7; Sony, Tokyo, Japan) was used to capture the images (Figure 1).

Statistical analysis

All the data obtained was analyzed with a Statistical Package for the Social Sciences (SPSS) version 23 (IBM, New York, USA), using one-way analyses of variance (Anova) test and Least Significance Different (LSD). Significant differences were considered to be present if $P < 0.05$.

Results

Table 1 shows the mean and standard deviation (SD) of TNF- α , MDA in macrophage cells, and CGRP in sensory nerve cells expressions. Six h of LPS induction in group C resulted in a significantly increased expression of TNF- α and CGRP compared to group N, while the application of 25 ppm of topical EGCG hydrogels (T1) and 75 ppm EGCG hydrogels (T2) to the tooth cavities significantly inhibited the TNF- α and CGRP expressions compared to group C ($P < 0.05$). While TNF- α expression in T2 group was significantly lower than in T1 group, there was no significant difference in the decrease of CGRP expression between groups T1 and T2. MDA expression showed no significant difference in groups N, C, T1, and T2. The expression of TNF- α , MDA and CGRP can be seen in Figure 1.

Discussion

This study found that 6 h of dentinal application of LPS to the tooth cavities of Wistar rats (C group) caused an increase of TNF- α and CGRP expressions compared to normal teeth with healthy pulps (group N), while there was no significant increase in MDA expression. The results showed that application of LPS to cavity preparation for 6 h caused a pulpal inflammation with 2.5-fold increase of TNF- α expressions and 2.6-fold increase of CGRP expression compared to normal teeth with healthy pulps. The increase in TNF- α expression was caused by the ability of LPS to diffuse through the fluid movement of open dentinal tubules to reach the pulp chamber, triggering a cascade of pathological changes [2, 5].

Table 1. The mean (SD) of expression of TNF- α , MDA in macrophage cells and CGRP in sensory nerve cells after the application of 25 ppm and 75 ppm topical EGCG hydrogels

Groups	TNF- α	MDA	CGRP
N	3.17 (0.75) ^a	3.17 (0.75) ^a	2.33 (0.52) ^a
C	8.00 (0.89) ^c	3.37 (0.82) ^a	6.17 (1.17) ^b
T1	5.50 (1.52) ^b	3.40 (0.79) ^a	3.00 (0.89) ^a
T2	3.83 (0.75) ^a	3.39 (0.86) ^a	2.67 (0.82) ^a

Different superscript denotes a significant difference ($P < 0.05$)

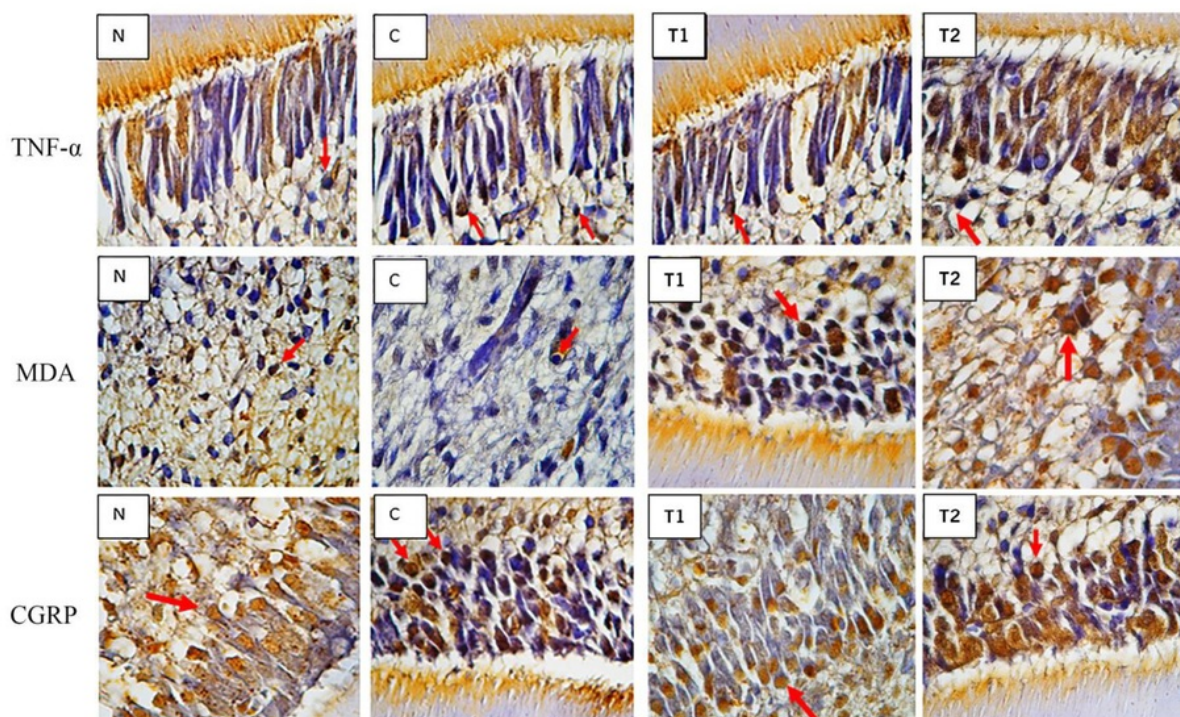


Figure 1. TNF- α , MDA in macrophage cells and CGRP in sensory nerve cells expression for normal healthy pulp (group N), 6 h LPS-induced inflamed pulp (group C), and after the application of 25 ppm (T1 group) and 75 ppm (T2 group) topical EGCG hydrogels. The red arrows indicate positive expressions

There was 2.6-fold significant increase in CGRP expression compared to normal teeth with healthy pulp group. The increase in CGRP expression was caused by the ability of TNF- α to indirectly or directly activate the sensory neuron cells via the release of prostaglandin (PG), leukotrienes and cytokines [28]. It leads to the opening of Na⁺ ion channel and stimulates the expression of CGRP [7, 8, 18, 29]. This result was in accordance with the previous studies which proved that there was an increase of CGRP expression in the initial stages of pulpal inflammation, which occurred 1 h after the injury and caused pain impulse conduction along the sensory nerve membrane [8-10, 30].

There was no significant difference in MDA expression at 6 h pulpal inflammation compared to normal teeth with healthy pulp group, possibly due to the limited duration of the inflammation causing extensive damage to the cell membrane. High level of ROS could damage the phospholipid membrane, which leads to MDA and arachidonic acid (AA) production [31]. In this case, after 6 h of inflammation, the level of ROS was still too low to begin the damaging process of PUFA, marked by no MDA level increase observed.

The application of 25 ppm and 75 ppm topical EGCG hydrogels to the tooth cavities of Wistar rats experiencing 6 h of pulpal inflammation caused a significant inhibition of TNF- α expression, consecutively 0.31-fold and 0.52-fold lower compared to control group with 6 h pulpal inflammation but received no topical EGCG hydrogels treatment. This was in accordance with the study carried out by Kim *et al.* [32] that confirmed the ability of EGCG in inhibiting TNF- α expression due to the interaction of EGCG with the protein and phospholipid of the plasma membrane, regulating the transduction signal and transcription factor, thus reducing NF- κ B activity. In addition, the study conducted by Jung *et al.* [33], showed that the application of EGCG on LPS-induced hPDLF caused a decrease in the number of IL-1 β , IL-6, TNF- α , osteoprotegerins (OPG) and receptor activators of nuclear factor kappa-B ligand (RANKL) and RANKL/OPG. The result showed that 75 ppm topical EGCG had a better property in inhibiting TNF- α expression compared to those of 25 ppm, which indicated that the higher concentration of EGCG would lead to a higher inhibition of TNF- α expression. The results from the present

study were consistent with Khan *et al.* [34], which confirmed that galloyl and hydroxyl group of EGCG would inhibit gene transcription to release TNF- α . Higher number of galloyl groups in catechin caused a stronger ability in binding free radicals, resulting in higher inhibition of TNF- α [35].

The application of both 25 ppm and 75 ppm topical EGCG hydrogels significantly inhibited the expression of CGRP, compared to control group, but have no significant difference compared to normal teeth with healthy pulp group. This was possibly due to the application of EGCG which inhibits TNF- α expression [18, 29]. CGRP has little effect on the inflammatory changes of the dental pulps, but it is involved in reparative inflammatory process of pulp [11].

In contrast, there was no significant difference in MDA expression in normal teeth, in teeth with 6-h inflammation and in teeth treated with 25 and 75 ppm of EGCG hydrogels for 2×24 h. MDA expression is a marker of cell membrane damage. It is possibly due to the limited duration of the inflammation, which caused no damage in cell membrane resulting in minimal MDA expression. The minimal MDA expression was also showed in C group after 6 h pulpal inflammation. There was a significant decrease in TNF- α expression between treatment groups, which suggested that the applications of 75 ppm topical EGCG hydrogels produced a superior anti-inflammatory effect by inhibiting TNF- α expression, compared to those of 25 ppm. However, there was no significant difference in expression of CGRP and MDA between 25 ppm and 75 ppm of EGCG hydrogels groups.

Conclusion

The application of 75 ppm topical EGCG hydrogels to the tooth cavities of Wistar rats with 6 h of pulpal inflammation has the optimal result in reducing the expression of TNF- α and CGRP, but could not inhibit MDA. Considering the EGCG components like polyphenolic substances can be used for various purposes in endodontics and would have a promising role in future medicine as well as dentistry.

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Conflict of Interest: 'None declared'.

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